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TITLE: Immunotoxins for treatment of intracranial lesions and as adjunct to chemotherapy

DATE-ISSUED: October 4, 1994

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/183.1; 424/832, 514/12, 514/21, 514/8, 530/391.7, 530/394

CLAIMS:

We claim:

1. A method of treating central nervous system tumors or prophylaxing against metastatic lesions to the central nervous system comprising administering a tumor-inhibiting amount of a conjugate comprising a diphtheria toxin, wherein said diphtheria toxin lacks an active cell binding activity, attached to a moiety which binds to transferrin receptors, wherein said moiety which binds to transferrin receptors is selected from the group consisting of an anti-transferrin receptor antibody and transferrin, and wherein the mode of administration is intracranial or intrathecal.

2. A method of treating central nervous system tumors according to claim 1, wherein said mutant diphtheria toxin is selected from the group consisting of CRM102, CRM103 and CRM107.

3. A method of treating central nervous system tumors according to claim 2, wherein said mutant diphtheria toxin is CRM103.

4. A method of treating central nervous system tumors according to claim 2, wherein said mutant diphtheria toxin is CRM107.

5. The method of claim 1, wherein the conjugate is administered intrathecally.

6. The method of claim 1, wherein the conjugate is administered intraventricularly.

7. The method of claim 1, wherein the conjugate is administered into the cavity left by a surgical resection of the tumor.

8. The method of claim 1, wherein the central nervous system tumor treated or the metastatic lesion to the central nervous system prophylaxed against are secondary tumors arising from a primary breast malignancy.

9. The method of claim 1, wherein the central nervous system tumor treated or the metastatic lesion to the central nervous system prophylaxed against are secondary tumors arising from a primary lung malignancy.

10. The method of claim 1, wherein the central nervous system tumor treated or the metastatic lesion to the central nervous system prophylaxed against are secondary tumors arising from a primary prostate malignancy.

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L3: Entry 236 of 246 File: USPT Aug 11, 1998

US-PAT-NO: 5792458
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TITLE: Mutant diphtheria toxin conjugates

DATE-ISSUED: August 11, 1998

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/183.1; 424/155.1, 424/174.1, 424/832, 424/94.1, 514/12, 530/350, 530/387.7, 530/391.7

CLAIMS:

What is claimed is:

1. A toxin conjugate comprising (i) a mutant diphtheria toxin, wherein said mutant diphtheria toxin has a cell surface receptor binding site that binds to said cell surface receptor with an affinity lower than that of wild-type diphtheria toxin and a translocation function, and has an amino acid point mutation of serine residue 508 or of serine residue 525, covalently attached to (ii) a binding moiety which binds to a specific receptor;

wherein said translocation function is measured by a cytotoxicity assay using said conjugate and a cell expressing said specific receptor.

2. A toxin conjugate according to claim 1, wherein said mutant diphtheria toxin has a serine to phenylalanine mutation at residue 508.

3. A toxin conjugate according to claim 1, wherein said mutant diphtheria toxin has a serine to phenylalanine mutation at residue 525.

4. A toxin conjugate according to claim 1, wherein said binding moiety is transferrin.

5. A toxin conjugate according to claim 1, wherein said binding moiety is a monoclonal antibody which specifically binds to the T3 antigen receptor on human T-cells.

6. A toxin conjugate according to claim 1, wherein said binding moiety is epidermal growth factor.

7. A toxin conjugate according to claim 1, wherein said binding moiety is a monoclonal antibody that specifically binds to transferrin receptor.

8. A method for the treatment of graft versus host disease which comprises:

i) obtaining bone marrow cells from a donor;

ii) incubating said bone marrow cells with an immunotoxin according to claim 1; and

iii) injecting said bone marrow cells treated in step (ii) into an irradiated recipient.

9. The method of claim 8, wherein said binding moiety is transferrin or a monoclonal antibody that specifically binds to a transferrin receptor.

10. A method for selectively removing T cells from a sample of bone marrow cells which comprises incubating said bone marrow cells with an immunotoxin according to claim 1.

11. A method according to claim 10, wherein the binding moiety of said immunotoxin is a monoclonal antibody.

12. The method of claim 11, wherein said monoclonal antibody is a monoclonal antibody which specifically binds to the T3 antigen receptor on human T-cells.

13. A method for selectively killing leukemia cells, which comprises contacting said leukemia cells with an immunotoxin according to claim 1, wherein the binding moiety of said immunotoxin is a monoclonal antibody which specifically binds to the T3 antigen receptor on human T-cells.

14. The method of claim 13, wherein said mutant diphtheria toxin contains a point mutation of serine residue 508 to phenylalanine or a mutation of serine residue 525 to phenylalanine.

15. A toxin conjugate according to claim 1, wherein said mnutant diphtheria toxin has an amino acid point mutation of serine residue 508.

16. A toxin conjugate according to claim 1, wherein said mutant diphtheria toxin has an amino acid point mutation of serine residue 525.

17. A toxin conjugate according to claim 1, wherein said specific receptor is resident on the surface of a target cell.

18. A method for enhancing the selectivity of a mutant diphtheria toxin which comprises covalently attaching (i) a mutant diphtheria toxin, wherein said mutant diphtheria toxin has a cell surface receptor binding site that binds to said cell surface receptor with an affinity lower than that of wild-type diphtheria toxin and a translocation function, and having an amino acid point mutation of serine residue 508, or an amino acid point mutation of serine residue 525, to (ii) a binding moiety which binds to a specific receptor;

wherein said translocation function is measured by a cytotoxicity assay using said conjugate and a cell expressing said specific receptor.

19. The method according to claim 18, wherein said binding moiety is selected from the group consisting of transferrin, a monoclonal antibody and epidermal growth factor.

20. The method of claim 19, wherein the binding moiety is transferrin.

21. The method of claim 19, wherein the binding moiety is a monoclonal antibody which specifically binds to transferrin receptor.

22. The method of claim 19, wherein the binding moiety is epidermal growth factor.

23. The method of claim 19, wherein the binding moiety is a monoclonal antibody which specifically binds to the T3 antigen receptor on human T-cells.

24. A method according to claim 18, wherein said specific receptor is resident on the surface of a target cell.

25. A toxin conjugate comprising (i) a binding moiety which specifically binds to a receptor of a cell of a neural cell tumor, a glial cell tumor, a metastatic small cell lung carcinoma or metastatic breast carcinoma tumor and (ii) a mutant diphtheria toxin, wherein said mutant diphtheria toxin consists of an A chain polypeptide and a B chain polypeptide, wherein said B chain polypeptide has a cell surface receptor binding site that binds to said cell surface receptor with a binding affinity lower than that of wild-type diphtheria toxin and an A chain translocating activity, and wherein said B chain has an amino acid point mutation of serine residue 508 or of serine residue 525, wherein said binding moiety is covalently linked to said mutant diphtheria toxin;

wherein said A chain translocating activity is measured by a cytotoxicity assay using said conjugate and a cell expressing said specific receptor.

26. A toxin conjugate of claim 25, wherein said cell is a glioblastoma or medulloblastoma cell.

27. A toxin conjugate of claim 25, wherein said mutant diphtheria toxin has a point mutation of serine residue 508 to phenylalanine or of serine residue 525 to phenylalanine.

28. A toxin conjugate of claim 25, wherein said receptor is a transferrin receptor.

29. A toxin conjugate of claim 28, wherein said binding moiety is transferrin or a monoclonal antibody which specifically binds to a transferrin receptor.

30. A toxin conjugate according to claim 25, wherein said specific receptor is resident on the surface of a target cell.

31. A toxin conjugate comprising (i) a mutant diphtheria toxin, wherein said mutant diphtheria toxin has a cell surface receptor binding site that binds to said cell surface receptor with an affinity lower than that of wild-type diphtheria toxin and has a point mutation of serine residue 508 and a point mutation of proline residue 308, covalently attached to (ii) a binding moiety which binds to a specific receptor.

32. A toxin conjugate according to claim 31, wherein said mutations of serine residue 508 and of proline residue 308 change said serine residue 508 to phenylalanine and change said proline residue 308 to serine.

33. A toxin conjugate according to claim 31, wherein said binding moiety specifically binds to the T3 receptor on human T cells.

34. A method for selectively removing T cells from a sample of bone marrow which comprises incubating said bone marrow cells with an immunotoxin according to claim 31.

35. A toxin conjugate according to claim 31, wherein said binding moiety is one that specifically binds to the transferrin receptor.

36. A method for selectively killing leukemia cells, which comprises contacting said leukemia cells with an immunotoxin according to claim 33.

37. A toxin conjugate according to claim 33, wherein said binding moiety is a monoclonal antibody that specifically binds to the T3 antigen of T cells.

38. A toxin conjugate comprising (i) a mutant diphtheria toxin, wherein said mutant diphtheria toxin consists of an A chain polypeptide and a B chain polypeptide, wherein said B chain polypeptide has a cell surface receptor binding site that binds to said cell surface receptor with a binding affinity lower than that of wild-type diphtheria toxin and has a point mutation of serine residue 508 and a point mutation of proline residue 308, covalently attached to (ii) a binding moiety which specifically binds to a receptor of a cell of a neural cell tumor, a

glial cell tumor, a metastatic small cell lung carcinoma or a metastatic breast carcinoma tumor.

39. A toxin conjugate according to claim 38, wherein said mutations of serine residue 508 and of proline residue 308 change said serine residue 508 to phenylalanine and change said proline residue 308 to serine.